

Value of cardiac magnetic resonance imaging in systemic sclerosis

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Abstract

Objectives: To assess the prevalence and patterns of cardiac abnormalities as detected by cardiac magnetic resonance imaging (MRI) in systemic sclerosis.

Material and methods: Twenty-six consecutive patients with systemic sclerosis underwent cardiac MRI to determine morphological, functional, perfusion at rest, and delayed enhancement abnormalities.

Results: At least one abnormality on cardiac MRI was observed in 19/26 (73%) patients. Increased myocardial signal intensity in T2 was observed in 10 patients (38.5%), thinning of the left ventricular myocardium in 1 patient (3.5%), and pericardial effusion in 12 patients (46%). Left and right ventricular ejection fractions were altered in 10 patients (38.5%) and 11 patients (42%), respectively. Myocardial delayed contrast enhancement was found in 11 (42%) patients. No perfusion defects at rest were found. Patients with limited systemic sclerosis had similar cardiac MRI abnormalities to patients with diffuse systemic sclerosis. Four out of 11 patients (36.4%) without pulmonary arterial hypertension had right ventricular dilatation.

Conclusions: The present study shows that cardiac MRI is an accurate and reliable technique to diagnose cardiac involvement in systemic sclerosis and to analyze precisely its mechanisms, including inflammatory, microvascular and fibrotic components. As it is non-invasive, quantitative and highly sensitive, cardiac MRI appears to be a method of choice to determine the natural history of untreated patients or to accurately monitor the effects of treatment. Moreover, it could provide powerful prognostic factors in both groups. Compared to echocardiography, cardiac MRI appears to provide additional information by visualizing myocardial fibrosis and inflammation. Finally, the present study has shown that RV dilatation is not specific for pulmonary arterial hypertension and could correspond to a specific heart involvement in systemic sclerosis.

Key words: myocardial fibrosis, diffuse systemic sclerosis, cardiac magnetic resonance imaging.

Introduction

Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by widespread microvascular damage and fibrosis of the skin and various internal organs, including the heart [1]. In necropsy series, myocardial fibrosis was reported in 50–80% of cases [2, 3]. It accounts for a substantial portion of cardiac mortality [4]. Myocardial fibrosis is the pathological hallmark of this complication and has been reported in 50–80% of cases in

autopsy studies, whereas it is rarely clinically obvious [2, 3]. The main limitation of the routine methods assessing heart involvement such as echocardiography is that they are not specific for myocardial fibrosis [5, 6].

Cardiac magnetic resonance imaging (MRI) is a recent, accurate and sensitive method to study heart structure and function non-invasively and precisely [7, 8]. Previous studies have shown that cardiac MRI is helpful in the diagnosis of acute inflammatory myocarditis [9] and myocardial fibrosis [6–9]. The aims of the present study were to

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assess the usefulness of cardiac MRI in systemic sclerosis (SSc), focusing either on delayed contrast enhancement abnormalities, or on ventricular volumes and ejection fractions and myocardial perfusion at rest.

Material and methods

Patient population

This retrospective study included 26 patients with SSc who underwent cardiac MRI between February 2013 and September 2016. In all patients, the diagnosis of SSc was based on standard classification criteria [10]. Patients with a history of coronary artery disease or cardiomyopathy were excluded. The study was approved by the institutional review board, and informed consent was obtained from all patients.

Clinical assessment gathered data on age at onset of the first symptom of SSc except Raynaud's phenomenon, age at onset of Raynaud's phenomenon, and cutaneous extension graded according to the LeRoy classification [11]. Overt coronary arterial disease was excluded based on clinical examination and a systematic ECG.

All patients underwent Doppler echocardiography performed by a cardiologist. Pulmonary arterial hypertension (PAH) was suspected in patients with a peak velocity of tricuspid regurgitation (VTR) > 2.5 – 3 m/s and unexplained dyspnea, or with VTR > 3 m/s, and warranted confirmatory right heart catheterization [12]. Left ventricular (LV) systolic dysfunction was defined as an LV ejection fraction (LV EF) $\leq 45\%$.

Cardiac magnetic resonance imaging

None of the patients had any contraindications for a cardiac MRI, especially renal insufficiency, which has been involved in nephrogenic systemic fibrosis. The examination was performed on a 1.5 Tesla MR scanner (Siemens Medical Solutions, Erlangen, Germany).

The cardiac MRI protocol included an ECG-triggered dark-blood-prepared half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence (TR/TE, 2 heartbeats/60 ms; flip angle, 160°) covering the entire heart in the axial orientation. Thereafter, four-chamber and two-chamber views as well as contiguous short-axis images of the entire heart were acquired with a fast imaging steady-state free precession (trueFISP) cine sequence (3 ms/1.5 ms; flip angle, 60°). Images in the oblique orientation were obtained to further investigate suspicious areas. Immediately after the injection of 0.2 mmol/kg of gadolinium diethylene triamine pentaacetic acid (Magnevist; Schering, Berlin, Germany) (flow rate, 2 ml/sec), breath-hold ECG-triggered 2D inversion recovery turbo FLASH images (8/4; flip angle, 25°) of four-

and two-chamber views of the heart were acquired. Repeated three-dimensional (3D) inversion recovery turbo FLASH sequences (4/1.4; flip angle, 10°) in the short-axis orientation were then performed. In patients with suspicious findings, additional oblique slices were obtained, using either the 2D or the 3D inversion recovery turbo FLASH sequence. Images were acquired both immediately after injection of the contrast material and as long as 15 minutes after the injection (myocardial delayed enhancement). Whereas the 2D sequence is a single-slice technique (slice thickness, 8 mm), the 3D sequence can acquire as many as 24 slices with a slice thickness of 4 mm in one breath-hold of reasonable length, using a shorter TR, partial Fourier reconstruction (6/8), z-axis interpolation, and a longer data acquisition window, with 77 k-space lines per heartbeat to improve speed. The total imaging time required, including patient positioning, was 45–60 min. All MR images were interpreted by an experienced radiologist who was unaware of the diagnosis and of the results of the echocardiographic examinations. The interpretations for the HASTE, trueFISP, and conventional DE-CMR, DE-CMR long inversion time were performed separately.

Imaging data analysis

The myocardium was studied in 17 segments according to the American Heart Association (AHA) standardized myocardial segmentation [13]. The morphological study assessed the presence of increased intra-myocardial signal intensity on T2-weighted images. A thickness ≤ 4 mm was considered as a thinned myocardium. RV hypertrophy was defined by a thickness ≥ 5 mm. The presence of LV and/or RV dilatation was defined as an increased indexed LV and/or RV end-diastolic volume when compared to available normal values [14–16]. An impaired LV or RV ejection fraction was defined according to normal values provided by Kawel-Bhoehm et al. [14]. Delayed contrast enhancement was defined as an area fulfilling all of the following criteria: a signal intensity value > 2 SD above the normal myocardium [16], presence in the same myocardial segment in at least two different planes, and presence in identical planes on two different acquisitions, with the appropriate inversion time.

Statistical analysis

All data are presented as mean \pm SD or as frequencies, i.e. n (%). Comparisons of means were performed with the non-parametric Wilcoxon test, comparisons of frequencies with the chi-square or Fisher exact tests. Correlations between numerical parameters were evaluated using Pearson's correlation. Statistical analyses

Table I. Clinical characteristics of systemic sclerosis population

Factor	
Women/men, <i>n</i>	21/5
Age, years	51 ±12
Limited/diffuse cutaneous SSc, <i>n</i>	16/10
Disease duration since first non-Raynaud's phenomenon, years	6.2 ±5.8
Disease duration since Raynaud's phenomenon, years	10.9 ±9.8
Interstitial lung disease on HRCT, <i>n</i> (%)	14 (54)
Precapillary pulmonary arterial hypertension by right heart catheterization, <i>n</i> (%)	6 (23)
Hypertension	8
Current smokers	0
Diabetes mellitus	2
Body mass index > 27	0

Data are mean ±SD or absolute number (%); HRCT – high-resolution CT of the chest

were performed with SAS software (version 9.1, SAS Institute Inc., Cary, NC, USA).

Results

Clinical characteristics

The clinical characteristics of patients are shown in Table I. No patient had overt left heart failure.

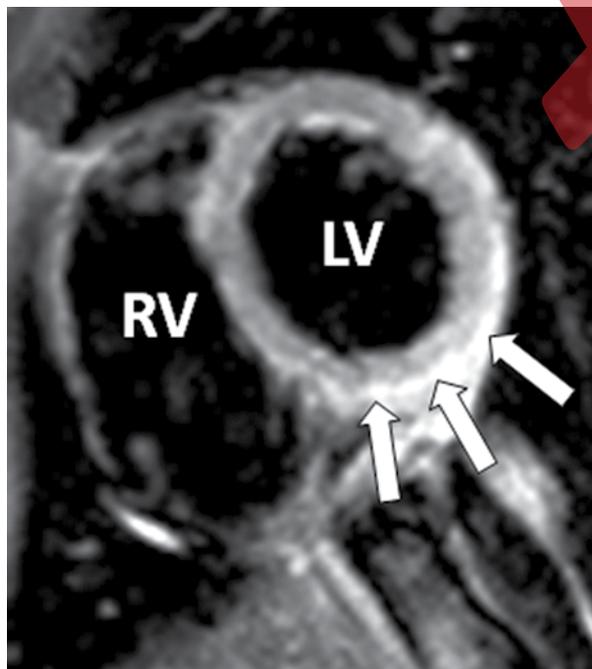


Fig. 1. Cardiac magnetic resonance imaging of a 52-year-old woman with systemic sclerosis. Abnormal increased signal intensity on T2-weighted sequences is shown (arrows).

Pattern and distribution of cardiac magnetic resonance imaging abnormalities

Morphological study

Increased signal intensity on T2-weighted sequences was found in 10/26 (38.5%) patients (Fig. 1). Mean duration of SSc was not significantly lower in patients with increased signal intensity (mean ±SD: 6.8 ±6.5 vs. 4.5 ±3.9 years, $p = 0.28$). Thinning of the LV myocardium was observed in 1/26 (3.5%) patient. Left ventricular dilatation and RV dilatation were found in 10/26 (38.5%) and 19/26 (73%), respectively. The RV was hypertrophied in 15/26 (57.6%) patients. Pericardial effusion was observed in 12/26 (46%) patients.

Perfusion analysis

No perfusion defect at rest was detected by visual analysis.

Functional study

Ten out of 26 (38.5%) patients had an impaired LV ejection fraction (mean ±SD: 43 ±7%) and 11/26 (42.3%) patients had an impaired RV ejection fraction (mean ±SD: 35 ±9%), without evidence of overt cardiac failure in any patient. Left ventricular kinetic abnormalities were found in 12/26 (46%) patients, mainly global LV hypokinesia ($n = 10$) and more rarely segmental LV hypokinesia ($n = 2$). Global RV hypokinesia was observed in 11/26 (42.3%) patients.

Myocardial delayed enhancement

Myocardial delayed enhancement was detected in 11/26 (42.3%) patients. It was subepicardial enhance-

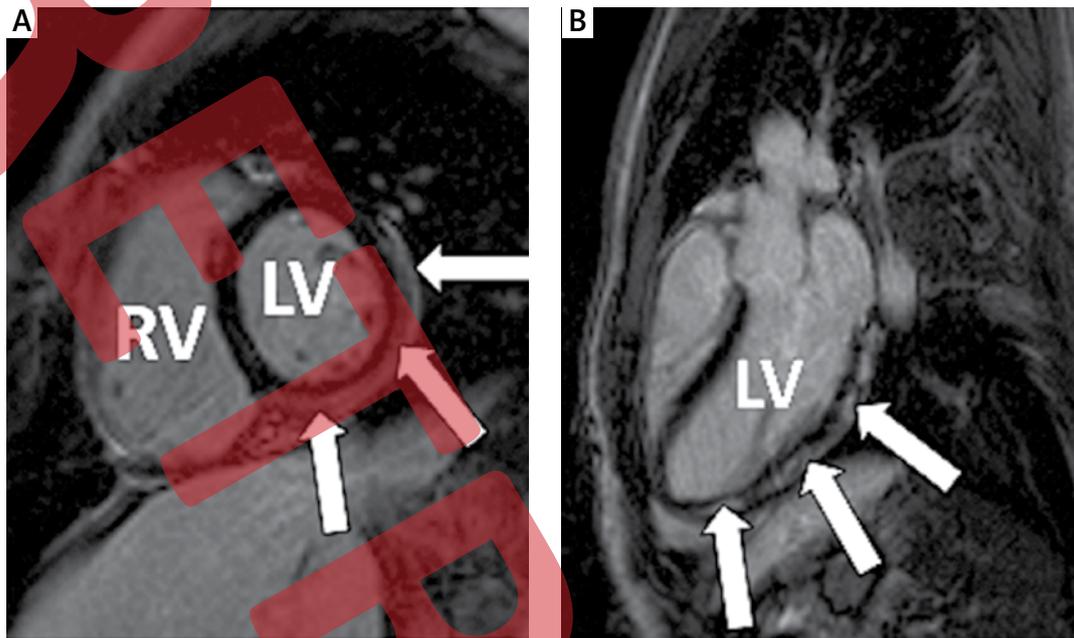


Fig. 2. Cardiac magnetic resonance imaging of a 48-year-old woman with systemic sclerosis. Short-axis (A) and three-chamber (B) views showing subepicardial myocardial delayed enhancement of the lateral and inferior wall of the left ventricle (arrows).

ment pattern in the majority of patients ($n = 8/11$) and more rarely mid wall ($n = 1/11$) or transmural ($n = 1/11$) (Fig. 2). There was no correlation with any coronary artery distribution.

Correlation between cardiac magnetic resonance imaging abnormalities

Among the 10 patients with increased signal intensity on T2-weighted sequences, 2 patients also had myocardial delayed enhancement. All of the 11 patients with myocardial delayed enhancement had LV kinetic abnormalities.

Association between cardiac magnetic resonance imaging abnormalities and clinical presentation of systemic sclerosis

A comparison of cardiac MRI findings between patients with limited cutaneous and patients with diffuse cutaneous SSc showed no differences between the 2 subtypes except for the frequency of impaired LV ejection fraction. A comparison of cardiac MRI findings between patients with and patients without precapillary PAH was done. Mean pulmonary arterial pressure was 35 ± 14 mmHg and mean cardiac index was 2.89 ± 0.94 l/min/m². Eleven patients with RV dilatation had undergone a right heart catheterization to exclude the

presence of either precapillary PAH or postcapillary pulmonary hypertension. Four patients had RV dilatation but without PAH, and 2 also had LV dilatation. Concerning the duration of SSc before cardiac MRI, we found that the longer the disease duration from the first non-Raynaud's phenomenon symptom was, the greater was the number of cardiac segments presenting kinetic abnormalities ($r = 0.29$; $p < 0.05$) and delayed contrast enhancement ($r = 0.30$; $p < 0.05$). With Raynaud's phenomenon as the first sign of SSc, we found that the longer the disease duration was, the greater was the number of cardiac segments presenting kinetic abnormalities ($r = 0.35$; $p < 0.05$). No correlation was found with delayed contrast enhancement ($r = 0.19$; $p = 0.15$).

Association between cardiac magnetic resonance imaging abnormalities and echocardiographic findings

Sensitivity of cardiac MRI to detect cardiac abnormalities was 21/26 (81%) as compared to 11/26 (42%) for echocardiography. Among the 10 patients with LV dilatation on cardiac MRI, four also had LV dilatation on echocardiography. Among the 19 patients with RV dilatation on cardiac MRI, five also had RV dilatation on echocardiography. Mean LV ejection fraction obtained by echocardiography was significantly higher than LV

ejection fraction obtained by MRI ($63 \pm 7\%$ vs. $60 \pm 9\%$, $p < 0.05$).

Discussion

The main results of our study are as follows. Firstly, a large majority (81%) of SSc patients had at least one abnormality on cardiac MRI, which gives a higher sensitivity than echocardiography (42%). Secondly, cardiac MRI enabled us to analyze precisely the different patterns of heart involvement in SSc by differentiating morphological, functional, perfusion and delayed contrast enhancement abnormalities. Thirdly, limited cutaneous SSc patients had roughly the same MRI abnormalities as diffuse cutaneous SSc patients and RV dilatation was not specific for PAH. The high frequency of heart abnormalities observed on cardiac MRI is consistent with autopsy studies which showed that about 80% of SSc patients had histological lesions of heart involvement [2, 3].

As in previous studies [17–19] this complication was rarely detectable at the bedside as in the present study. Taken together, these results suggest both that such alterations are clinically underestimated and that cardiac MRI is highly sensitive. Yet, the clinical significance of cardiac MRI abnormalities remains to be established. The present study enabled the different patterns of cardiac involvement in SSc to be distinguished using cardiac MRI. Previous studies have shown that cardiac MRI can accurately detect myocardial fibrosis [7, 18]. In the case of myocardial fibrosis, the gadolinium is trapped in the fibrosis, whilst it is washed more rapidly in the normal myocardium, explaining the myocardial delayed enhancement. The myocardial delayed enhancement observed in the present study had almost the same characteristics as those of Tzelepis' study, with the same predominance of a midwall and linear pattern [4]. Lesions of the small coronary arteries or arterioles were recorded in about 20% of autopsy cases [2]. In chronic infarction, myocardial remodeling results in regional thinning of the myocardium. Thinning of the LV observed in the present study could therefore reflect the chronic coronary microvascular injury related to SSc. Finally, inflammation is likely to play a role in SSc as well as in cardiac involvement [19, 20].

Increased signals on T2-weighted images are indicators of soft tissue edema [6–8]. In the absence of any correlation with coronary artery distribution, increased signal intensity in T2-weighted images is suggestive of inflammatory myocarditis [20, 21].

In the past, edema could not be used as a diagnostic tool because even histology failed to provide reliable information on its presence. Extensive studies have confirmed a close correlation between T2-weighted signal intensity

and edema [22]. Adding T2-weighted images to a standard cardiac MRI protocol (function, perfusion, and scar) increased the specificity, positive predictive value, and overall accuracy for detection of an acute coronary syndrome from 84% to 96%, 55% to 85%, and 84% to 93%, respectively [23]. Furthermore, using late gadolinium enhancement (LGE), cardiac MRI not only detects myocardial infarction in as little as 1 cm^3 of tissue, substantially less than other in vivo methods, but also has excellent agreement with histology in animal and human studies [24, 25].

Finally, cardiac MRI was also proven useful in detecting small myocardial scars and diffuse subendocardial fibrosis that were missed by other imaging techniques. Even a small area of LGE ($< 2\%$ of LV mass) was associated with a > 7 -fold increase in risk for a major adverse cardiac event [26].

The present study also showed that LV and/or RV ejection fractions were altered in 11 patients although the mean values remained within the normal range and patients had no evidence of overt cardiac failure. The alteration of LV and RV ejection fractions is most likely a direct consequence of myocardial fibrosis, as previously suggested [27, 28].

We did not find any perfusion defect on cardiac MRI in patients with SSc. This is consistent with the absence of increased coronary artery arteriosclerosis in SSc [2]. However, we must acknowledge that our technique may have lacked sensitivity [29], precluding the possibility to see perfusion defects usually observed using thallium perfusion scans [30]. Interestingly, we found no great differences in terms of cardiac MRI abnormalities between patients with limited cutaneous and patients with diffuse cutaneous SSc. These results are consistent with a previous study, where heart symptoms were not found to be significantly different between the two subtypes [1].

The present study found that LV ejection fraction was more often altered in patients with limited cutaneous SSc, although no patients had overt cardiac failure and mean values remained in the normal range.

In the present study, up to 21% of patients without PAH had RV dilatation. It is worthy of note that all these patients underwent right heart catheterization to rule out PAH. This is further evidence for the specific RV involvement in SSc, most likely related to myocardial fibrosis. PAH was rather mild in the present study, probably explaining why some patients with PAH had no RV dilatation. Concerning the comparison of data provided by echocardiography and cardiac MRI, the present study shows that cardiac MRI provides additional information. Some analyses were not possible by echocardiography, most notably myocardial delayed enhancement, increased signal intensity and thinned myocardium. However, echocardiography is more useful in valvular heart

diseases, especially in PAH screening with tricuspid gradient evaluation. The present study shows that patients with a longer disease duration had more kinetic abnormalities and myocardial delayed enhancement, which is consistent with previous studies [7, 8, 18]. These results suggest progression of myocardial fibrosis over time and therefore a natural history of heart involvement in SSc. This natural history could be longitudinally studied by repeated cardiac MRI.

We acknowledge that the present study has some limitations. There was no histological confirmation of the present study imaging data, since this procedure was judged to be too invasive to be incorporated into our study. We did not include a control group of healthy subjects, thus precluding any firm conclusions regarding the higher frequency of abnormalities. Results from a 3 Tesla (3T) MRI might have provided more detailed information on the extent of fibrosis and its morphology. We did not systematically measure brain natriuretic peptide or troponin levels.

Conclusions

The present study shows that cardiac MRI is an accurate and reliable technique to diagnose cardiac involvement in SSc and to analyze precisely its mechanisms, including inflammatory, microvascular and fibrotic components. As it is non-invasive, quantitative and highly sensitive, cardiac MRI appears to be a method of choice to determine the natural history of untreated patients or to accurately monitor the effects of treatment. Moreover, it could provide powerful prognostic factors in both groups. Compared to echocardiography, cardiac MRI appears to provide additional information by visualizing myocardial fibrosis and inflammation. Finally, the present study has shown that RV dilatation is not specific for PAH and could correspond to a specific heart involvement in SSc. Further studies are now required to determine whether cardiac MRI abnormalities have a significant clinical impact on both prognosis and treatment strategy.

The authors declare no conflict of interest.

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